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George A. Frank
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ALAN GEWIRTZ

Appeal 2009-006223
Application 09/993,183
Technology Center 1600

Decided: February 24, 2010

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for anticipation and obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF CASE

The following claims are representative.

1. A method for disrupting expression of a mammalian target gene at the mRNA level in a human cell, wherein the method comprises initiating RNA interference (RNAi) *in vitro* by exposing the human cell to a double-stranded RNA (dsRNA) homologous to the target gene, wherein the dsRNA consists essentially of two complementary linearized strands of RNA, the transcription of each is independently controlled to generate paired RNAs of defined length.

22. A method for disrupting expression of a mammalian target gene in vitro in a human cell, wherein the method comprises providing an RNA sequence homologous to a portion of a target gene, said RNA capable of inducing RNAi of the target gene.

23. The method of claim 22, wherein the target gene is c-kit and the RNA is KdsRNA in an amount effective to induce RNA interference, thereby disrupting expression of-the target gene.

Cited References

Fire et al. (Fire '559)	US 6,506,559 B1	Jan. 14, 2003
Gewirtz et al.	WO 92/19252	Nov. 12, 1992
Kreutzer et al.	WO 00/44895	Aug. 3, 2000

Phillip A. Sharp, *RNAi and double-strand RNA*, 13 GENES & DEVELOPMENT 139-141 (1999).

Appellant relied on the following references:

Kreutzer et al.	US 2004/0175703 A1	Sept. 9, 2004

Andrew Fire (II), *RNA-triggered gene silencing*, 15 TRENDS IN GENETICS 358-363 (1999).

Mary K. Montgomery and Andrew Fire, *Double-stranded RNA as a mediator in sequence-specific genetic silencing and co-suppression*, 14 TRENDS IN GENETICS 255-258 (1998).

Florence Wianny and Magdalena Zernicka-Goetz, *Specific interference with gene function by double-stranded RNA in early mouse development*, 2 NAT. CELL BIOL. 70-75 (2000).

Paddison et al., *Stable suppression of gene expression by RNAi in mammalian cells*, 99 PROC. NAT'L ACAD. SCI. 1443-1448 (2002).

Svoboda et al, *Selective reduction of dormant maternal mRNAs in mouse oocytes by RNA interference*, 127 DEVELOPMENT 4147-4156 (2000).

Declaration of Dr. Alan M. Gewirtz, submitted September 14, 2005.

Declaration of Dr. Alan M. Gewirtz for Earlier Date of Invention, submitted April 28, 2006.

Grounds of Rejection

1. Claims 1, 2, 5, 7-9, 11, 21,22, and 24-27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Fire '559.

2. Claims 1, 2, 5, 7-9, 11, and 21-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire '559 as applied to claims 1, 2, 5, 7-9, 11, 21, 22, and 24-27 in the §102(e) rejection, Gewirtz (WO 92/19252) and Sharp.

FINDINGS OF FACT

The findings of fact below are applicable to the rejections of record.

1. The Examiner finds that, Fire '559 discloses "a method for inhibiting expression of a target gene using double stranded RNA to induce RNAi in a cell in *vitro* (Column 26, claim 1) wherein the cell is from an animal (Column 26, claim 6)." (Ans. 4.)

2. The Examiner finds that:

> Fire ['559] disclose that the cell with the target gene may be derived from or contained in any organism (column 8, line 13-

> 14) and that examples of vertebrate animals include mammals and human (column 8, lines 35-37) and that the cell having the target gene may be "immortalized or transformed, or the like" (column 8, lines 52-55) and that "the present invention could be used for treatment or development of treatments for cancers of any type, including solid tumors and leukemias. . ." (Column 10, lines 26-28).

(*Id.*)

3. The Examiner finds that:

> Fire ['559] disclose that lipid mediated carrier transport can be used to introduce nucleic acids to cells (Column 9, lines 55-60). Fire ['559] also disclose that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene (Column 6, lines 55-57), thereby indicating disruption of gene function (which is to produce protein).

(Ans. 4-5.)

4. The Examiner finds that "the limitation 'selecting a human cell expressing the target gene' is not defined in the specification, so for prior art purposes, this recitation is being interpreted to mean a cell line that contains a target gene and is capable of being treating with a dsRNA" (*id.* at 5-6).

5. "Fire ['559] teach target genes that are oncogenes (col. 11)." (Ans. 6.)

6. The Examiner finds that:

> Fire ['559] also teach that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene as determined by measurement of the target gene or expression from said target gene (Column 6, lines 55-57), thereby indicating disruption of gene function (which is to produce protein).

(*Id.*)

7. The Examiner finds that:

> Fire ['559] teach that using the methods of their invention, gene disruptions may be used to discover the function of a target gene and to produce disease models in which the target gene is involved in causing or preventing a pathological condition (col. 5, lines 30-37). Fire ['559] disclose that relative to antisense approaches, their invention has advantages in the stability of the material to be delivered (col. 3, line 20).

(*Id.*)

8. "Fire ['559] do not teach the nucleotide sequence of the oncogene c-Kit." (*Id.*)

9. "Gewirtz et al. teach the antisense inhibition of c-Kit proto-oncogene expression in human cells and that c-kit antisense oligonucleotides are particularly useful against leukemia and melanoma (see page 15, lines 6-25)." (*Id.*)

10. "Gewirtz et al. disclose that the c-Kit cDNA sequence was known in 1987 and cite Yarden et al. Gewirtz et al. do not specifically teach inhibition in HL-60 cell lines or CHP 100 cell lines." (Ans. 6.)

11. "Sharp is added as a general reference supporting the idea that RNAi is a general mechanism that is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes." (*Id.* at 7.)

12. The Examiner concludes that:

> It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to substitute an dsRNA oligonucleotide in place of the antisense oligonucleotide in a method of inhibiting the expression of the oncogene c-Kit *in* vitro using an antisense inhibitor in human leukemia cells (as taught by Gewirtz et al.),

> wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire ['599]) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because dsRNA can be used to initiate RNA interference *in vitro* by targeting oncogenes in human cells including leukemia (as taught by Fire ['599]) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire ['599]).

(*Id.*)

13. The Examiner concludes that:

> [I]t would have been further obvious to use a HL-60 cell line for the study of leukemia in vitro and further obvious to use CHP 100 to study the cellular events associated with neuroblastoma. Fire ['559] does not specifically disclose the optimal time of incubation of said dsRNA with a cell or the optimal concentration of dsRNA used but it would have been obvious to one of skill in the art and a matter of routine optimization to determine the amount of time to expose the dsRNA to the cell to achieve the most efficient gene interference and to determine the optimal workable ranges of a dsRNA that most efficiently caused gene interference in a cell. MPEP 2144.05 states in part "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

(Ans. 7-8.)

14. The Examiner concludes that:

> One of ordinary skill in the art would have been motivated to practice a method of inhibiting the expression of the oncogene c-Kit in *vitro* in human leukemia cells or melanoma cells (as taught by Gewirtz et al.) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in

> pharmaceutical composition (as taught by Fire ['559]) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered and has advantages of sequence specificity (as taught by Fire ['559]).

(*Id.* at 8.)

15. The Examiner finds that:

> One of ordinary skill in the art would have expected success in practicing a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells (as taught by Gewirtz et al.) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire ['559]) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because Fire ['559] teach that dsRNA can be used to initiate RNA interference in human cells and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire ['559]).

(Ans. 8-9.)

16. The Examiner finds that "it is not disputed that Fire ['559] et al. did not exemplify his invention in human cells, but just because Fire ['559] did not reduce to practice his invention does not mean the invention was not enabled." (*Id.* at 10.)

17. The Examiner finds that:

> Since the issuance of the Fire ['559]. . ., which is presumed to be enabled, thousands of post-filing art references have repeatedly shown that the methods of Fire et al. ['559] work in

> human cells. In fact, Fire et al. won a Nobel Prize for their discovery, largely based upon the implications of its use in humans, and the discovery that the process underlies an entire RNA-dependent system of gene regulation that is conserved at some level across virtually every multi-cellular organism (see Zamore, Nat. Struct. Biol. From the IDS for review).

(Ans. 10.)

18. Fire II, Trends in Genetics 1999 (Exhibit I, Evidence Appendix), states that, with regard to medical applications involving targeted silencing of renegade genes, that "[a]lthough this hope is not ruled out by any current data, the simple protocols used for invertebrate and plant systems are unlikely to be effective. Mammals have a vehement response to dsRNA, the best-characterized component of which is protein kinase (PKR) that responds to dsRNA by phosphorylating (and inactivating) translation factor EIF2a …" (Page 363.)

19. The Examiner finds that the "paragraph cited by Appellant is not evidence that Fire felt his invention was limited to invertebrate animals and his thoughts on whether this would work was mere speculation and was not an admission by Fire as alleged by Appellant." (Ans. 10-11.)

20. The Examiner finds that, to the contrary, "this mere speculation has proved to be unfounded given the voluminous amount of post-filing art that has shown the methods of Fire ['559] work in human cells." (*Id.* at 11.)

21. Wianny shows that dsRNA can be used as a specific inhibitor of gene activity in mouse oocyte and preimplantation embryo. (Wianny, 73, right col.)

22. Wianny disclosed that concerns in Fire II, Trends Genetic 1999 that RNAi might not work in the mouse may have been raised prematurely. (*Id.*)

23. Wianny discloses that dsRNA is specific to the corresponding gene and it does not cause a general translation arrest, because embryos continue to develop without signs of cell death. (Wianny, 73, right col.)
24. Wianny states that "natural" dsRNA may be less effective at inducing PKR, and the degree of induction could vary between cell types, in which case RNAi would be effective. (*Id.*)
25. Wianny states that they anticipate that dsRNA mediated inhibition of gene expression should be equally effective in other mammals, including both domestic animals and humans. (Wianny, 74, left col.)
26. Svoboda confirmed the results in Wianny and demonstrated that RNAi is an effective and efficient method to inhibit the translation of maternal messenger RNAs that are recruited in oocyte maturation in the mouse. (Svoboda, 4153, right col.)
27. Paddison acknowledged the early successful results of Wianny and Svoboda in injection dsRNA into early stage mouse embryos and the achievement of DNA silencing. (Paddison, 1445, left col.).

Discussion

1. Claims 1, 2, 5, 7-9, 11, 21, 22, and 24-27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Fire ['559].

ISSUE

The Examiner argues that Fire '559 teaches each element of the claimed method, including practice of the method *in vitro* and *in vivo,* and describes its applicability to transformation of human cells. The Examiner argues that Fire '559 is presumed to be enabled.

Appellant contends that Fire '559 is a non-enabled anticipatory reference with respect to the human cells claimed.

The issue is: Has Appellant demonstrated error in the Examiner's anticipation rejection and has Appellant rebutted the presumption that Fire '559 is an enabling anticipatory reference by a preponderance of the sufficient evidence?

PRINCIPLES OF LAW

In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *See In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

In patent prosecution the Examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue. *In re Sasse*, 629 F.2d 675, 681 (CCPA 1980) ("[W]hen the PTO cited a disclosure which expressly anticipated the present invention … the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a preponderance of the evidence." [Emphasis added]. The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled. *Id. See also Amgen Inc. v. Hoescht Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Thus, "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled," which

appellants "can then overcome [ ] by proving that the relevant disclosures of the prior art patent are not enabled." *Id.*

In the infringement setting,

> Like the applicant in *ex parte* prosecution, … the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art. If a patentee presents evidence of nonenablement that a trial court finds persuasive, the trial court must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption has been overcome.

Id.

Prior art is not enabling so as to be anticipating if it does not enable a person of ordinary skill in the art to carry out the invention. *See Elan Pharms., Inc. v. Mayo Found. For Medical Educ. And Research*, 346 F.3d 1051, 1057 (Fed. Cir. 2003).

Appellant can carry its burden of lack of enablement only by showing that all of the disclosed alternative modes are insufficient to enable the claims, because "'[t]he enablement requirement is met if the description enables any mode of making and using the invention.'" *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (quoting *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991)).

A patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Elan Pharms., Inc.*, 346 F.3d at 1054. "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. *In re Hafner*, . . . 410 F.2d 1403 (Cust. & Pat.App.1969)." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005).

"[S]ection 112 'provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure.' *Hafner*, 410 F.2d at 1405." *Id.* Thus, "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation. . . . [T]he proper issue is whether the [prior art] is enabling in the sense that it *describes* the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) (emphasis added). A prior art reference is anticipatory under 35 U.S.C. §102(b) if it discloses each and every element of the claimed invention, either explicitly or inherently, and if it enables person of ordinary skill in art to make the invention without undue experimentation. *In re Gleave*, 560 F.3d 1331, 1337-8 (Fed. Cir. 2009).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").

Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to

make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

The examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605 (CCPA 1977).

If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms.

Principles of Law for remaining obviousness rejections

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we considered the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); (1) the scope and

content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

"[O]bviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

ANALYSIS

Appellant contends that Fire '559 is a non enabled reference with respect to the claimed method in human cells. (App. Br. 4.) Appellant contends that the Declaration evidence and other evidence of record supports that Fire '559 is not enabled for transformation of human cells with dsRNA. (App. Br. 12-14.) Appellant argues that Fire II summarizes the state of the art at that time of the Fire '559 application for patent and teaches that if RNAi existed in cells, "it would probably be necessary either to induce a transient lapse in PKR response, or to use a dose incapable of activating the PKR response to practice RNAi methods in mammalian cells. Yet Fire ['559] provides no guidance on any methods or means of inducing a lapse in the PKR response, nor were any methods predictable at the time of Appellant's filing." (App. Br. 11 (emphasis omitted).)

We have carefully considered all enablement related evidence of record, including Declaration evidence, and conclude that the Appellant has failed to rebut the presumption that the disclosure of the Fire '559 is enabled for transformation of human cells with dsRNA by a preponderance of the evidence.

In particular, the pending claims are limited to "initiating RNA interference *in vitro* by exposing the human cell to a double-stranded RNA … ." (Claim 1).

We find that while Fire II, *Trends in Genetics* (1999) may have speculated about the PKR response potentially interfering with *in vivo* medical applications using "simple protocols," Appellant has provided no evidence that one of ordinary skill in the art at the time of Fire '559's application filing would have believed that Fire '559 would not work in less complex *in vitro* applications using human cells, an application encompassed by claim 1. Appellant provides no evidence that one of ordinary skill in the art, following the method set forth in Fire '559, would be unsuccessful at modifying human cells *in vitro*. Fire II says nothing about concerns related to *in vitro* applications of the method of Fire '559 in human cells.

If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d at 1562. However, in this case, we conclude that the speculative statements in Fire II do constitute evidence that the procedures outlined in the Fire '559 patent would not work. The statements made in Fire II were not based on any evidentiary data convincing to one of ordinary skill in the art and thus are not conclusive, but merely speculative statements. Later publications, such as Wianny, Svoboda and Paddison confirmed that the procedures outlined in Fire '559 would work in mammalian cells, and Wianny particularly stated regarding dsRNA-mediated inhibition of gene expression in the mouse, that "[w]e anticipate

that it should be equally effective in other mammals, including both domestic animals and humans." (Wianny, 74, left col.)

We have further reviewed the credentialed Declaration of Alan Gewirtz dated September 14, 2005, which provides a review of the evidence of record. The Declaration fails to account, however, for the legal presumption in this case and Appellant's burden to rebut the presumption of the Fire '559 patent's enablement. Furthermore, an anticipatory disclosure does not have to be reduced to practice, so the fact that data was never presented in Fire '559 showing the effect of dsRNA in vertebrate and human cells, as alleged by the Declarant, is not controlling. What is controlling is whether Fire '559 discloses each and every element of the claimed invention, which Appellant acknowledges in the Appeal Brief at page 7, and whether it enables person of ordinary skill in art to make the invention without undue experimentation. *In re Gleave*, 560 F.3d 1331, 1337-8 (Fed. Cir. 2009). Appellant has presented no evidence that one of ordinary skill in the art following the method set forth in Fire '559 would not have been able to transform human cells in vitro, and later publications, such as Wianny, Svoboda and Paddison, reasonably appear to confirm that the procedures outlined in Fire '559 would work in mammalian cells.

CONCLUSION OF LAW

We conclude that Appellant has failed to rebut the presumption that Fire'559 was enabled by a preponderance of evidence. Thus we conclude that a preponderance of the evidence supports that Fire '559 method was enabled for transformation of human cells *in vitro*, at the time of its filing.

2. Claims 1, 2, 5, 7-9, 11, and 21-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire '559 as applied to claims 1, 2, 5, 7-9, 11, 21-22 and 24-27 in the 102(e), Gewirtz (WO 92/19252) and Sharp.

ISSUE

Appellant contends that there would have been no expectation of success of practicing a method for inhibiting the expression of the oncogene c-kit in vitro in human leukemia cells (Reply Br. 18) and that the cited references do not teach each element claimed because Fire '559 does not teach transformation of human cells (Reply Br. 19). Appellant argues that there would have been no motivation to combine the cited references. (Reply Br. 22.)

We are not persuaded. For the reasons discussed herein with respect to Fire's ['559] disclosure of disclosure of the transformation of human cells, we conclude that Appellant has not provided sufficient evidence of lack of an enabling disclosure.

With respect to Appellant's argument concerning motivation to combine the cited references or resolve the issues in Fire '559 regarding RNAi in mammalian systems (App. Br. 23), the Examiner found that

> One of ordinary skill in the art would have expected success in practicing a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells (as taught by Gewirtz et al.) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire ['559]) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because Fire ['559] teach that dsRNA can be used to initiate RNA interference in human cells and because

> relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire ['559]).

(Ans. 8-9.)

We conclude that the Examiner has provided a rationale as to why one of ordinary skill in the art would have combined the cited references and that Appellant has not rebutted or countered this rationale by a preponderance of evidence.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

GEORGE A. FRANK
DRINKER BIDDLE & REATH LLP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA PA 19103-6996